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Profile of illness in Syrian refugees: A GeoSentinel analysis, 2013 to 2015

Mockenhaupt, Frank P ; Barbre, Kira A ; Jensenius, Mogens ; Larsen, Carsten S ; Barnett, Elizabeth D ; Stauffer, William ; Rothe, Camilla ; Asgeirsson, Hilmar ; Hamer, Davidson H ; Esposito, Douglas H ; Gautret, Philippe ; Schlagenhauf, Patricia

Abstract: Screening of 488 Syrian unaccompanied minor refugees (< 18 years-old) in Berlin showed low prevalence of intestinal parasites (*Giardia*, 7%), positive schistosomiasis serology (1.4%) and absence of hepatitis B. Among 44 ill adult Syrian refugees examined at GeoSentinel clinics worldwide, cutaneous leishmaniasis affected one in three patients; other noteworthy infections were active tuberculosis (11%) and chronic hepatitis B or C (9%). These data can contribute to evidence-based guidelines for infectious disease screening of Syrian refugees.

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Multidrug-resistant organisms detected in refugee patients admitted to a University Hospital, Germany June–December 2015

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Multidrug-resistant Gram-negative bacteria (MDR GNB) were found to colonise 60.8% (95% confidence interval: 52.3–68.9) of 143 refugee patients mainly from Syria (47), Afghanistan (29), and Somalia (14) admitted to the University Hospital Frankfurt, Germany, between June and December 2015. This percentage exceeds the prevalence of MDR GNB in resident patients four-fold. Healthcare personnel should be aware of this and the need to implement or adapt adequate infection control measures.

Current data provided by Federal Agency of Migration and Refugees, Germany, indicate a dramatic increase in migration, with most people arriving from Syria, Albania, Afghanistan and Iraq [1]. These countries are known as countries with high prevalence for multidrug-resistant Gram-negative bacteria (MDR GNB) (*Enterobacteriaceae*, *Acinetobacter baumannii*) and for methicillin-resistant *Staphylococcus aureus* (MRSA) [2–5]. People from these countries are thus at higher risk of being colonised with such pathogens and adequate infection prevention measures need to be taken to prevent spread in healthcare settings in the countries where they seek refuge. Systematic studies regarding prevalence of multidrug-resistant organisms (MDRO) in refugees are not yet available in the scientific literature. In order to fill this gap, we investigated the prevalence of MDR GNB and MRSA in patients admitted from refugee (REF) accommodations to the University Hospital Frankfurt am Main (UHF), Germany between June and December 2015 and compared it with prevalence in resident patients.

Investigation of prevalence of multidrug-resistant organisms in refugee and resident patients

At UHF, all patients admitted from hospitals in countries with high prevalence or from refugee accommodations are pre-emptively isolated and screened for MDRO on the day of admission. The same algorithm is

applied to resident patients with previous treatment in hospitals in countries with high prevalence for MDRO and all patients admitted to intensive/intermediate care units (ICUs/IMCs).

During the study period, REF patients were identified on admission and screened for MDRO by rectal swabs for MDR GNB and nasal swabs for MRSA. MDR GNB screening was undertaken for extended spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*, and *Enterobacteriaceae* and *Acinetobacter baumannii* resistant to piperacillin, any third generation cephalosporin, and fluoroquinolones +/- carbapenems.

Patients admitted to ICU/IMC within the same period were included as comparison group since these patients are routinely screened for MDRO. This group reflects the demographic and epidemiological characteristics of the resident population not admitted from a refugee accommodation (NREF).

Patients admitted from hospitals in countries with high prevalence for MDRO were excluded from the study.

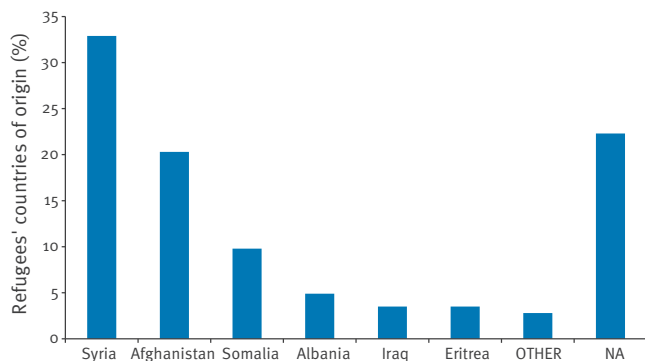
MDRO screening was done in accordance to German infection protection law and the infection control strategy at UHF. Ethical approval was given by Ethics Committee of the UHF.

Laboratory identification of multidrug-resistant bacteria

For detection of MDR GNB, rectal swabs were collected using Amies collection and transport medium (Hain Lifescience, Germany) and streaked onto CHROMagar™ ESBL plates (Mast Diagnostica, Paris, France). Identification of MDR GNB species was done by matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry. Antimicrobial susceptibility testing was performed using VITEK2 (bioMérieux, Nürtingen, Germany) according to Clinical

FIGURE

Countries of origin of refugees screened for multidrug-resistant Gram-negative bacteria and meticillin resistant *Staphylococcus aureus*, Frankfurt, Germany June–October 2015 (n=143)



OTHER are Pakistan, Moldavia, Lebanon, or Georgia.
NA: information about country of origin not available.

and Laboratory Standards Institute (CLSI) guidelines [Version M100-S25, 2015] and antibiotic gradient tests (bioMérieux).

Carbapenemase-encoding genes were detected via PCR analysis and subsequent sequencing from carbapenem-resistant *Enterobacteriaceae* including the *bla* genes for carbapenemases NDM, VIM, IMP, OXA-48, and KPC and OXA-23, OXA-24, OXA-51, and OXA-58 for *A. baumannii* [6,7]. Carbapenem-resistant *A. baumannii* isolates were assigned to international clusters by repetitive element sequence based-PCR (DiversiLab®, bioMérieux) [7,8].

For the detection of MRSA, moistened nasal swabs were inoculated on Brilliance MRSA Agar (Oxoid, Wesel, Germany) and identification and antimicrobial susceptibility testing were performed as described above. Clonal identity was determined by *staphylococcal protein A* (*spa*) typing using the Ridom StaphType software (Ridom GmbH, Würzburg, Germany) [9].

We used the biostatistical data file from University Münster, Germany for statistical analyses [10]. Confidence intervals (CI) were calculated based on binomial distribution and *p* values (2-tailed) of $p \leq 0.05$ were considered statistically significant.

Prevalence in refugee compared with resident patients

Multidrug-resistant Gram-negative bacteria

Between June and December 2015, a total of 143 REF and 1,489 NREF were screened for MDR GNB on day of admission. The average age in the two groups was 21.7 years (range 1–65, SD 16.4) for REF and 64 years (11–94; SD 16.2) for NREF, respectively. Of REF patients 84.6%

were male and of NREF 69.4%. REFs' countries of origin were not available for evaluation in 32 cases (22.4%) due to lacking records in patients' files (Figure).

Of the 143 REF samples 60.8% (for 95% CI and patient numbers see Table) were positive for any MDR GNB, significantly exceeding the rate in NREF (16.7%) ($p \leq 0.05$).

Among all MDR GNB species, ESBL-producing *Escherichia coli* were detected with higher prevalence in REF than in NREF (23.8 vs 4.9%). Prevalence of ESBL-producing *Klebsiella pneumoniae* exceeded the prevalence in NREF (4.2 vs 0.8%). Prevalence of ESBL-producing *E. coli* with additional resistance to fluoroquinolones was higher in REF than that in NREF (26.6 vs 6.9%) and ESBL-producing *K. pneumoniae* with additional resistance to fluoroquinolones were found in a higher proportion in REF compared with NREF (4.2 vs 1.9%). All results were statistically significant.

One REF carried three MDR GNB organisms: ESBL-producing *E. coli* with additional resistance to fluoroquinolones, ESBL-producing *K. pneumoniae* and carbapenem-resistant *A. baumannii*. Two REF were positive for two MDR GNB organisms each; one carried *E. coli* with additional resistance to fluoroquinolones and ESBL-producing *K. pneumoniae* with additional resistance to fluoroquinolones, one carried ESBL-resistant *E. coli* and ESBL-resistant *E. coli* with additional resistance to fluoroquinolones.

In REF, three carbapenem-resistant isolates were detected: one carbapenem-resistant *K. pneumoniae*, expressing VIM-1 which is frequently detected in southern Europe [11], and two carbapenem-resistant *A. baumannii* (1.4%), harbouring carbapenemases OXA-23 and OXA-24, respectively. Strain typing revealed that these isolates belong to international cluster II which is disseminated worldwide and is frequently associated with OXA carbapenemases [7,8].

In NREF, 16 (1.1%) carbapenem-resistant isolates were detected. Two of these were identified as *K. pneumoniae* expressing OXA-48, one expressed OXA-48 and NDM-1, and in seven isolates no specific carbapenemase gene was detected. Carbapenem-resistant *E. coli* isolates were detected in three cases with all of them expressing OXA-48. Carbapenem-resistant *Enterobacter cloacae* strains were detected in two cases with one expressing OXA-48 and one without specific carbapenemase gene detection. Carbapenem-resistant *A. baumannii* was detected in one case; no other carbapenemase than species-specific OXA-51 was detectable.

Meticillin-resistant *Staphylococcus aureus*

Screening for MRSA was performed for 143 REF and 1,170 NREF. In REF, eight MRSA isolates (5.6%; 95%CI: 2.5–10.7) were detected, which significantly exceeded the prevalence in NREF where 14 isolates were positive (1.2%; 95%CI: 0.6–2.0). *Spa* types in REF (n=1 not

TABLE

Distribution of multidrug-resistant Gram-negative bacteria in refugee compared with resident patients, Frankfurt, Germany July–December 2015

	Patients admitted from refugee accommodations (REF)		Resident patients not admitted from refugee accommodation (NREF)	
Total number of patients	143		1,489	
	% (n)	95% CI	% (n)	95% CI
Positive for MDR GNB ^a	60.8 (87)	52.3–68.9	16.7 (250)	14.9–18.8
<i>Escherichia coli</i> ESBL ^b	23.8 (34)	17.1–31.5	4.9 (73)	3.8–6.1
<i>Escherichia coli</i> ESBL/FQ ^b	26.6 (38)	19.5–34.6	6.9 (104)	5.7–8.4
<i>Escherichia coli</i> Carba	0.0 (0)	0.0–2.5	0.2 (3)	0.04–0.5
	Carbapenemases None		Carbapenemases OXA-48 (3)	
<i>Klebsiella pneumoniae</i> ESBL ^b	4.2 (6)	1.5–8.9	0.8 (12)	0.4–1.4
<i>Klebsiella pneumoniae</i> ESBL/FQ ^b	4.2 (6)	1.5–8.9	1.9 (28)	1.2–2.7
<i>Klebsiella pneumoniae</i> Carba	0.7 (1)	0.02–3.8	0.6 (10)	0.3–1.2
	Carbapenemases VIM-1(1)		Carbapenemases OXA-48 (2) OXA-48 and NDM-1 (1) No carbapenemase detected (7)	
<i>Enterobacter cloacae</i> Ceph/FQ	0.0 (0)	N.a.	0.5 (8)	0.2–1.1
<i>Enterobacter cloacae</i> Carba	0.0 (0)	N.a.	0.1 (2)	0.02–0.5
	Carbapenemases None		Carbapenemases OXA-48 (1) No carbapenemase detected (1)	
<i>Enterobacter aerogenes</i> Ceph/FQ	0.0 (0)	N.a.	0.2 (3)	0.04–0.5
<i>Citrobacter freundii</i> Ceph/FQ	0.0 (0)	N.a.	0.3 (4)	0.07–0.7
<i>Klebsiella oxytoca</i> Ceph/FQ	0.0 (0)	N.a.	0.06 (1)	0.002–0.3
<i>Acinetobacter baumannii</i> Ceph/FQ	0.0 (0)	N.a.	0.06 (1)	0.002–0.3
<i>Acinetobacter baumannii</i> Carba	1.4 (2)	0.2–0.5	0.06 (1)	0.002–0.3
	Carbapenemases ^c OXA-23 (1) OXA-24 (1)		Carbapenemases ^c No carbapenemase detected (1)	

Carba: resistance to carbapenems; ESBL: extended beta-spectrum lactamase-producing; FQ: resistance to fluoroquinolones; MDR GNB: multidrug-resistant Gram-negative bacteria.

^a Organism and resistance pattern.

^b Values in neighboring columns vary statistically significantly ($p \leq 0.05$).

^c Other than species-specific OXA-51.

determined) were t223 (n=2), t386, t790, t852, t1532, and t10343 (n=1 each) and *spa* types in NREF were t003 (n=8), t032 (n=2), t008, t012, t034, and t127 (n=1 each).

Discussion and conclusion

Having protocols in place to control infectious disease transmission in hospitals is good practice to ensure patient safety and should be the focus of preventive efforts. While travel to countries with high prevalence, medical tourism, or contact to local healthcare in such countries have been identified as contributing to the transmission and geographical spread of MDRO worldwide [2,3,5,12], considerations on limiting the spread of MDRO should be expanded to people coming from or passing through countries with high prevalence and seeking refuge, for example in Germany. In terms of hospital infection control strategies, this population

may represent a yet unidentified risk in countries with low endemicity.

Our study has revealed a strong link between the status REF and carriage of MDR GNB and MRSA exceeding that of NREF, which might constitute an inherent risk of introduction in another countries healthcare system, such as previously observed in Turkey, where NDM-1-producing *A. baumannii* strains were most likely imported from neighbouring Syria [13]. MRSA *spa* types detected in REF were less common in Germany whereas NREF colonised with MRSA were found to harbour *spa* types known to be most frequent in Germany [14].

According to the guidelines by the infection prevention commission (KRINKO) at the Robert-Koch Institute, Berlin, Germany, isolation is recommended for all hospitalised patients for the following patient groups: patients with MRSA [15] and patients with

carbapenem-resistant MDR GNB [16]. Additionally, in hospital units at high risk for nosocomial transmissions such as ICUs and IMCs, isolation of patients with MDR GNB resistant to cephalosporins and fluoroquinolones and/or MDR GNB with resistance to carbapenems is recommended. In our study the latter would apply to 32.9% of REF versus 10.9% of NREF patients. Taking all KRINKO guidelines (including MRSA) into account, a total of 38.5% of REF and 12.1% of NREF would qualify for isolation. The demonstrated high MDRO prevalence in our REF study population calls for intensive efforts in hospital hygiene to guarantee best medical practice for every single patient.

While it is hardly possible to predict any evolutionary or geographical success of these MDRO strains in German hospitals or elsewhere in Europe, our small-scale investigation provides some evidence for the importance of screening and aligned hygiene measures in patients admitted from refugee accommodations. It is hard to estimate the whether the REF population in the UHF setting is representative of the overall refugee population in Germany. However, a study also conducted in Frankfurt am Main but in unaccompanied refugee minors (<18 years- old) in refugee centres also found a high prevalence of ESBL-producing *Enterobacteriaceae* (35%) even though lower than that in our study [17].

One limitation of our study may be the pre-selection of NREF. As mentioned above, this group consists of patients admitted to ICUs and IMCs: considering that they are critically ill, possible prior antibiotic treatment might have resulted in increased prevalence of MDRO in the NREF group used for comparison. This might lead to an overestimation of the MDRO prevalence in our NREF group and thus to an underestimation of the difference in MDRO prevalences between REF and NREF patients.

Unfortunately, information regarding refugees' itineraries were not available due to missing records in the patient files and the language barrier on hospital admission. Such information, however, would help to better understand the origin and transmission routes of MDROs. For example refugees might have acquired a particular MDRO during their transit through a country with high prevalence. Future investigations on clonal relatedness and comparisons with major endemic clones should allow to analyse the spread of MDRO in connection with the movements of refugees.

At UHF, all REF are screened for MDRO and pre-emptively isolated on the day of admission. In case of negative screening results, REF are released from isolation. In case of positive MDR GNB and/or MRSA results, REF remain in isolation during their entire stay. Since June 2015, this procedure has been implemented and guarantee best medical practice for every individual patient at UHF, independently of their country of origin.

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Authors declare that this report is exclusively based on epidemiological findings and is not influenced by any political opinion. Authors furthermore confirm that all patients are treated equally and in conditions of best medical care at UHF, regardless of their origin. Stephan Göttig and Volkhard A. J. Kempf were supported by a grant from the Deutsche Forschungsgemeinschaft (DFG—research unit 2251).

Conflicts of interest

The authors declare that they have no competing interests.

Authors' contributions

CR: compiling and interpretation of the data, manuscript writing. VK: interpretation of the data, manuscript writing. SG, MH, TW: generation and interpretation of the data, manuscript writing. FOR: manuscript review. CB: compiling and interpretation of the data, manuscript writing. All authors read and approved the final manuscript.

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